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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,809	05/01/2001	Olga Bandman	PF-0358-2 DIV	7331

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EXAMINER
CARLSON, KAREN C

ART UNIT	PAPER NUMBER
1653	10

DATE MAILED: 08/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/847,809	Applicant(s) BANDMAN ET AL.	
	Examiner Karen Cochrane Carlson, Ph.D.	Art Unit 1653	

-- The MAILING DATE f this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10, 29-37, 38-42* is/are pending in the application.

4a) Of the above claim(s) *29,32,34,35 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,30,31,33,36,37 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

This Office Action is in response to Paper #9, filed June 13, 2003.

Claims 1-9, 11-28, and 45-48 have been canceled. Claims 29, 32, 34, 35, 38 have been withdrawn from further consideration at this time by the Examiner because these Claims are drawn to non-elected inventions. Claims 10, 30, 31, 33, 36, 37, and 39-42 are currently under examination.

Priority is to August 8, 1997.

Withdrawal of Rejections

The rejection of Claims 10, 30, 31, 33, 36, 37, and 39-42 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is withdrawn.

Maintenance of Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36 and 39 are again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 36 and 39 depend from non-elected inventions. Therefore, these claims are indefinite.

Applicants urge that the amendment to Claim 10 limiting the antibody to specifically binding SEQ ID NO: 3 should place the antibody in condition for allowance and therefore rejoinder of the methods of making the antibody; thus, Applicants have opted not to place the

limitations of currently non-elected claims into Claims 36 and 39. As noted in the previous Office Action, the Examiner agrees with this premise. However, art remains against the claimed antibody.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 30, 31, 33, 36, 37, and 39-42 are again rejected under 35 U.S.C. 102(a) as being anticipated by Yabe et al. (July 18, 1997; J. Biol. Chem. 272:18323-18239) teach calumenin having 98.2% identity to SEQ ID NO: 3. On page 18234, col. 1, para. 3, Yabe et al. made antibodies against calumenin, anti-protein-disulfide isomerase antibody. Given that antibodies bind epitopic structures rather than sequences per se, and the identity between RCN□ and calumenin is high, the antibody made by Yabe et al. will also bind polypeptides having SEQ ID NO: 3 (Claim 10, 30, 36, 39). At page 18234, col. 1, para. 3, the antibodies were in composition (Claim 31, 37, 40). The antibodies were labeled via conjugation with fluorescein isothiocyanate (Claim 33). Claims 41 and 42 are being considered to be anticipated as well because there appears to be no difference in the antibody made by a Fab expression library or and immunoglobulin expression library.

Applicants urge that limiting the antibody to one that specifically binds SEQ ID NO: 3 overcomes the teachings of Yabe et al. Applicants argue that so long as there are differences

in the amino acid sequence of Yabe et al. and in instant SEQ ID NO: 3, an antibody can be produced that can specifically bind to SEQ ID NO: 3 and not to calumenin as taught in Yabe et al. Upon perusal of the sequence alignment attached to Yabe et al., it is noted that of the 315 amino acids of SEQ ID NO: 3, only 3 non-conservative amino acid mismatches exists. The 3 conservative amino acid mismatches are noted, but conservative amino acid substitution retains structure, including epitopic structure, and therefore these 3 conservative mismatches are not the focus of this argument. The differing amino acid residue at positions 183 and 195 are in a structurally nondescript region between EF-hands 3 and 4. The differing amino acid residue at position 224 is also in a structurally nondescript region between EF-hands 4 and 5. While a change in amino acid in an epitopic structure may prevent antibody formation, with such high identity between calumenin and SEQ ID NO: 3, it appears that the epitopic structure of one will be the same as the other and generate the same antibody. Therefore, the antibody taught in Yabe et al. is the same antibody claimed. It is noted that Applicants do not have an antibody that specifically binds to SEQ ID NO: 3 and no other protein in hand. If just an antibody is in hand, this rejection could be overcome by declaration.

Further, as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan (J. Histochem. Cytochem. 1995; 43:881-886), an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" with both proteins. For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross react with irrelevant peptides (e.g., "Results, page 579).

Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless

able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph).

Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444) teaches single amino acid substitutions outside the antigenic site on a protein effect antibody binding; thus it is also essential to provide some guidance as to the identity of the flanking sequences of a fragment of a polypeptide of interest. Further, Li et al. (Proc. Natl. Acad. Sci. USA 77: 3211-3214, 1980) disclose that dissociation of immunoreactive from other biological activities when constructing analogs (see entire document).

Thus in the absence of sufficient guidance to a particular epitope and the structural context in which the epitope is found; it is highly unpredictable which other isolated polypeptides comprising a variant sequence of SEQ ID NO:2 would maintain the relevant antibody epitope(s).

See also U.S. Pat. No. 6210670 (Berg) entitled "Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin".

Applicant's argument attempts to limit the term "specifically reacts" in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific.

Claims 10, 30, 31, 33, 36, 37, and 39-42 are again rejected under 35 U.S.C. 102(b) as being anticipated by Ozawa et al. (1993; J. Biol. Chem. 268:699-705). Ozawa et al. teach reticulocalbin having 89.1% identity to SEQ ID NO: 3. See the alignment attached to the reference. On page

700, col. 2, para. 3, Ozawa et al. made antibodies against reticulocalbin. Given that antibodies bind epitopic structures rather than sequences per se, and the identity between RCN□ and reticulocalbin is high, the antibody made by Ozawa et al. will also bind polypeptides having SEQ ID NO: 3, 90% identity to SEQ ID NO: 3, biologically active fragments of SEQ ID NO: 3, and immunogenic fragments of SEQ ID NO: 3 (Claim 10, 30, 36, 39). At page 700, col. 1, para. 4, the antibodies were in composition (Claim 31, 37, 40). At page 700, col. 2, para. , the antibodies were labeled via conjugation with fluorescein isothiocyanate (Claim 33). Claims 41 and 42 are being considered to be anticipated as well because there appears to be no difference in the antibody made by a Fab expression library or and immunoglobulin expression library.

Applicants urge that limiting the antibody to one that specifically binds SEQ ID NO: 3 overcomes the teachings of Ozawa et al. Applicants argue that so long as there are differences in the amino acid sequence of Ozawa et al. and in instant SEQ ID NO: 3, an antibody can be produced that can specifically bind to SEQ ID NO: 3 and not to reticulocalbin as taught in Ozawa et al. Upon perusal of the sequence alignment attached to Ozawa et al., it is noted that of the 315 amino acids of SEQ ID NO: 3, only 17 non-conservative amino acid mismatches exists. The 19 conservative amino acid mismatches are noted, but conservative amino acid substitution retains structure, including epitopic structure, and therefore these 19 conservative mismatches are not the focus of this argument. While a change in amino acid in an epitopic structure may prevent antibody formation, with such high identity between reticulocalbin and SEQ ID NO: 3, it appears that the epitopic structure of one will be the same as the other and generate the same antibody. Therefore, the antibody taught in Ozawa et al. is the same antibody claimed. It is noted that Applicants do not have an antibody that specifically binds to SEQ ID NO: 3 and no other protein in hand. If just an antibody is in hand, this rejection could be overcome by declaration. Applicants are also referred to the above discussion for "specifically binding".

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D. whose telephone number is 703-308-0034. The examiner can normally be reached on 7:00 AM - 4:00 PM, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low can be reached on 703-308-2329. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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July 9, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER